To: Chairman Davis and Committee on Government Reform Majority Members
From: Committee on Government Reform Majority Staff
RE: Response to Minority's Summary of FDA Documents
Date: November 17, 2004

Last week, Chairman Davis, Majority and Minority staff traveled to London. The CODEL was scheduled pursuant to the Committee's investigation into the October 5, 2004 Chiron manufacturing license suspension and the resulting U.S. flu vaccine shortage. The CODEL met with the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) and Chiron. After returning from London, a Committee meeting was held with U.S. Food and Drug Administration (FDA) to review documents obtained by the Chairman and Mr. Waxman as a result of the investigation and the information obtained while on the CODEL.

Today Mr. Waxman will distribute a 13-page memo to the Committee's Minority Members titled "Summary of FDA Documents." The memo is extremely misleading. FDA documents are taken out of context. Explanations provided to the Committee as to documents written and actions taken by MHRA, FDA, and Chiron are ignored by the Minority. The Minority has chosen to ignore standard FDA protocol, accepted by vaccine manufactures worldwide. The Minority's memo places the sole blame for the U.S. flu vaccine shortage on FDA, yet another partisan attack on the Administration, rather than taking an objective look at all the facts presented during the Committee's investigation.

Response to Minority's Memo

FDA standard protocol is to inspect overseas manufacturing facilities every two years. FDA conducted a standard inspection of Chiron's Fluvirin facility in June 2003. Upon being notified of Chiron's license suspension on October 5, 2004, FDA conducted another, not previously scheduled, inspection of the Fluvirin facility.

After an inspection, FDA provides the manufacturer with a Form 483. The Form 483 lists FDA's findings and provides a framework for the manufacturer to take corrective measures based on FDA's findings. FDA provided the Committee with the Form 483 from its June 2003 and October 2004 inspections.

A Form 483 is highly technical and scientific. It would be highly difficult for an individual without a graduate degree in science and familiarity with FDA protocol to interpret a Form 483. The Minority's superficial conclusions reflect this point. The Minority has chosen to pick and choose particular sentences from a detailed 7-page findings of FDA's June 2003 Form 483 to draw a causal connection between the FDA's findings in 2003 with Chiron's license suspension. In particular, the Minority cites that the June 2003 Form 483 refers to elevated levels of "bioburden" in vaccine pools, contamination by *Serratia* bacteria, deficiencies in the plant's "asceptic connections," improper sanitary practices, and inadequate efforts to investigate and correct sources of contamination at the Fluvirin facility. Because the Minority identified the same words

contained in FDA's 10-page October 2004 Form 483, they find it appropriate to imply that "widespread problems at the facility in June 2003 . . . recurred in 2004 and contributed to the closure of the facility."

In fact, this connection between the findings of the June 2003 inspection and Chiron's license suspension has been disputed by MHRA, FDA, and Chiron. In each meeting, it was explained that while FDA may have found similarities in the condition of the Fluvirin facility in June 2003 and October 2004, **the cause of Chiron's license suspension was a direct result of systemic problems within the facility, based upon a lack of manufacturing oversight and execution. In fact, Chiron's license was not suspended based upon contamination in flu vaccine lots or issues addressed subsequent to the June 2003 inspection.**

The Minority continues to mislead Committee Members regarding Chiron's June 2003 inspection with its analysis of a handwritten note by John Eltermann, Director of the Division of Manufacturing and Product Quality in FDA's Center for Biologics, Evaluation and Research. In the note, Mr. Eltermann has written "Tbio – OAI → VAI downgraded." "Tbio" stands for "team biologics," the FDA officials who conduct inspections of vaccine manufacturing facilities. "OAI" stands for "official action indicated," and "VAI" stands for "voluntary action indicated." Standard protocol for a team biologics is to recommend an FDA response to an inspection. The team biologics then meets with officials from FDA to discuss its recommendation and make a final decision. FDA told the Committee that the team biologics initially recommended an official action after Chiron's June 2003 inspection, but upon further discussion and a review of Chiron's written response to the June 2003 Form 483, it was agreed by all parties within FDA to issue a voluntary action.

The Minority chose to frame this process as FDA officials "rejected" the team biologics recommendation. However, as the Committee learned from FDA, it is not uncommon for the team biologics to make one recommendation and upon further discussion, alter its recommendation. The team biologics participates fully in the decision making process. It is irresponsible to suggest that a collaborative professional decision made by FDA officials and inspectors is a causal connection to lack of oversight by FDA and ultimately led to Chiron's license suspension.

The Minority informs its Members that FDA never reinspected the Chiron Fluvirin facility after the June 2003 inspection to determine if existing problems were resolved. This lack of inspection contributed to Chrion's license suspension. Again, this attempt at creating a causal connection between FDA's actions and Chiron's license suspension is not only irresponsible, but grossly misleads Members as to standard FDA procedures.

FDA inspects foreign facilities once every two years. A manufacturer is provided with a Form 483 at the conclusion of the inspection. The manufacturer then responds to the Form 483. This response includes the manufacturer's plans to remedy the issues highlighted by FDA as weaknesses in the Form 483. If FDA reviews and accepts the

manufacturer's response, the file is considered closed. FDA will then conduct another inspection within two years and will assess whether the manufacturer has dealt appropriately with the issues raised during the previous inspection.

On June 27, 2003, Chiron sent a letter to FDA. The letter stated that Chiron wanted to meet with FDA as soon as possible to discuss its response plan and its new Quality Systems Improvements Program. FDA did not respond to the letter, as it accepted Chiron's response to the June 2003 Form 483. In a September 3, 2003 closing letter, FDA informed Chiron it would review the manufacturer's corrective actions at its next inspection. When the Committee asked Chiron about the June 27, 2003 letter, Chiron officials did not recall sending such letter or its contents. FDA explained to the Committee that manufacturers frequently send follow up letters to their response plans asking for a meeting. It is customary that if FDA accepts the manufacturer's response plan, a meeting is unnecessary. Clearly, Chiron did not persist on a meeting with FDA, as no additional letters were sent prior or after the September 3, 2003 closing date.

The Minority attempts to paint a picture of a lackadaisical Agency that had no desire to follow-up on a manufacturer's progress. FDA was following standard, across the board protocol. In fact, FDA was allowing Chiron the time it needed and is customarily provided to manufacturers to implement its corrections.

In its attack of FDA's actions, the Minority claims that FDA remained passive, while MHRA was proactive, upon learning on August 25, 2004 that some lots of Chiron's Fluvirin were contaminated. This is not accurate. There was a team of FDA officials at Chiron's Liverpool facility for an unrelated issue on August 25, 2004. FDA asked the team to visit the Fluvirin portion of the facility to gauge the situation. In addition, FDA alerted the Centers for Disease Control and Prevention and conducted weekly conference calls with Chiron to continue oversight of the situation.

When a vaccine manufacturer identifies contamination within its facility, it initiates an internal investigation to determine how the contamination occurred. Chiron initiated an internal investigation in April 2004, upon discovering contamination in some lots of Fluvirin. It is standard FDA protocol to use the internal investigative report as a tool when conducting an inspection. The report provides a roadmap for FDA to use to understand where the manufacturers stand with regard to problems at a facility.

Chiron informed FDA that it could not provide a draft report of its internal investigation until the week of October 4, 2004. FDA informed the Committee that providing the draft report by early October was within an acceptable timeframe. Upon receiving the draft report, FDA would analyze its findings and determine if an inspection of the Fluvirin facility was warranted. FDA did not receive Chiron's draft report until after the license suspension. **FDA instructed Committee staff that had the Agency received the draft report sooner, the Chiron facility would have been reinspected, whether or not MHRA suspended Chiron's manufacturing license. FDA identified severe weaknesses in Chiron's draft report and was not satisfied that Chiron properly addressed the cause behind the contamination.**

The Minority would like to paint the time between August 25 and the week of October 4, 2004 as time that FDA should have been reaching out to MHRA to determine what, if anything, they were doing with regard to Chiron. This assertion is misleading, as pursuant to the Medicines Act, MHRA is prohibited from sharing commercial information without consent from Chiron. By law, MHRA was conducting all of its actions independently from FDA. As both FDA and MHRA informed Committee staff, it is widely accepted and understood that the two Agencies do not discuss their own actions with regard to companies over which they each have jurisdiction. Since its license suspension, Chiron has permitted FDA and MHRA to communicate on all issues that concern Chiron. However, the Medicines Act is still in place in the United Kingdom.

The Minority is free to argue that they do not agree with the laws of the United Kingdom. But, to imply that FDA was passive by not urging MHRA to violate its own law, serves only to confuse those who are not well versed in FDA protocol and the United Kingdom's Medicine Act.

Of additional concern regarding the August 25 to the week of October 4, 2004 time frame, is the Minority's statements that MHRA was on top of the Chiron situation, in contrast to FDA's passiveness. This is misleading for several reasons. First, MHRA told Committee staff that it waited two weeks to respond after receiving Chiron's e-mail regarding contamination in the Fluvirin lots. Second, Chiron provided its draft internal investigation document to MHRA on September 24, 2004. The Minority may highlight that MHRA read the draft report and followed up with an investigative visit to Chiron's Fluvirin facility. The truth is that MHRA wanted to review Chiron's draft report prior to conducting its final investigative visit of the facility. Once MHRA received the draft report, a team returned to the facility on September 28-30, 2004. As Chiron claimed it couldn't provide the draft report to FDA until the week of October 4, 2004, FDA's follow up inspection of the Fluvirin facility was prolonged. **The Minority misleads Members in asserting that FDA was not conducting the same oversight as MHRA. In fact, the Chiron document both Agencies needed to proceed was provided to MHRA before FDA, hindering FDA's ability to respond with an inspection as quickly as MHRA.**

The Minority draws attention to FDA documents that indicate FDA was working with Chiron to dispel fears of a vaccine shortage. This was the responsible action for both FDA and Chiron to take. Vaccinations and the availability of preventative medicines is an emotionally charged issue. The most productive way to handle any loss of vaccine availability is to educate the public and work to decrease fear of a widespread shortage. It would be irresponsible of FDA to not lay the groundwork for how to inform the U.S. public of the possibility of a vaccine shortage.

Although the flu investigation has been conducted in a bipartisan manner, the Minority's interpretation of the information obtained by the Committee is different from the Majority's. The investigation should not be a forum for bashing FDA for following its standard accepted protocols. FDA should not be held accountable for decisions made by Chiron without its knowledge or for actions taken by MHRA that were legally

protected by laws of the United Kingdom. If the Committee keeps looking back to place blame, we will be unable to look to the future to ensure the U.S. has an adequate flu vaccine supply. If protocols need to be tweaked, we should discuss tweaking them.

Chairman Davis' main goals in the Committee investigation are to understand the lessons learned from the Chiron's license suspension and work with U.S. health officials and private industry to ensure that a similar situation does not occur in the future. After his meetings with FDA, MHRA, and Chiron, the Chairman is optimistic that Chiron will be able to produce vaccine for next year's flu season. The Chairman also recognizes the U.S. must work to expand the number of flu vaccine manufacturers that are FDA approved, so that the U.S. has more than two major vaccine companies on which to rely.